

Understanding Immunotherapy and Lymphoma

The term immunotherapy refers to treatments that help promote the body's own immune response. The immune system is made of various cells, tissues, and organs that work together to fight off harmful pathogens, like bacteria and viruses, as well as cancers.

When the immune system is not working properly due to disease, immunotherapies may be given to restore its function. Immunotherapies may either stimulate or enhance parts or all of the immune system, enabling it to once again eliminate unwanted cells.

INTRODUCTION TO IMMUNOTHERAPY

IMMUNOTHERAPY AND CANCER

The immune system normally patrols the body for cancer cells. When a cancer cell is detected, the immune system launches an attack to eliminate it. However, some cancer cells are able to "hide" from or otherwise deceive the immune system, and can grow in an uncontrolled manner, until they form tumors or spread through the body (such as the case in lymphoma). Many cancers effectively shut down the immune system's ability to eliminate them. Immunotherapies help fight cancer by enhancing the immune system so that it can do its job and eliminate cancer cells from the body. Immunotherapy agents have been approved for the treatment of many types of cancer, including lymphoma.

IMMUNOTHERAPY AND LYMPHOMA

Immunotherapies have been used for the treatment of lymphoma for decades. Lymphoma occurs when cells of the immune system called lymphocytes, a type of white blood cell, grow and multiply uncontrollably. The body has two main types of lymphocytes that can develop into lymphomas: B lymphocytes (B cells) and T lymphocytes (T cells). Lymphoma cells tend to be sensitive to changes in the immune system, although this differs depending on the lymphoma subtype and between patients. Ultimately, how lymphomas respond to immunotherapy depends on how well the immune system can target the lymphoma cells.

IMMUNOTHERAPY AS A TREATMENT OPTION

BACKGROUND

Most immunotherapy drugs are given to patients in the same way as chemotherapy—orally (pill taken by mouth), subcutaneously (injection under the skin), or intravenously (injection directly into a vein). Immunotherapy drugs may even be given with chemotherapy, such as in the R-CHOP regimen (rituximab [Rituxan], cyclophosphamide, doxorubicin, vincristine, prednisone). Patients who have received catheters for chemotherapy may receive their immunotherapy through their catheter as well. For more information on chemotherapy regimens, view the fact sheet titled Getting The Facts – Chemotherapy on the Lymphoma Research Foundation's (LRF's) website at www.lymphoma.org/publications.

Oncology nurses are usually responsible for administering the immunotherapy prescribed by the doctor. Most patients receive their immunotherapy in an outpatient clinic, hospital outpatient department, or doctor's office. Sometimes patients have to stay in the hospital to receive their treatment.

Depending on the type of lymphoma, immunotherapies may be used as initial treatment for patients, for those with relapsed (disease returns) or refractory (disease no longer responds to treatment) disease. Several agents are approved by the U.S. Food and Drug Administration (FDA) for different lymphoma subtypes, and new unapproved immunotherapy medications and treatment regimens are being evaluated and may be given to patients in clinical trials. This fact sheet reviews immunotherapies that are currently used or being evaluated in the treatment of lymphoma.



OVERVIEW OF SPECIFIC THERAPIES

ANTIBODY-DRUG CONJUGATES

An antibody-drug conjugate (ADC) is a monoclonal antibody attached to a chemotherapy drug. These agents target lymphoma cells by attaching to a protein on the cell surface, such as CD30. The ADC then enters the cell, where the chemotherapy drug separates from the antibody portion and kills the cell by targeting a critical cell function, such as cell division. Similar to monoclonal antibodies, ADC is given intravenously. An example of an FDA-approved ADC is brentuximab vedotin (Adcetris). Side effects are caused both by the antibody and the chemotherapy portion of the drug, and may include low blood cell counts, nerve damage leading to neuropathy, anemia, fatigue, and nausea.

Brentuximab Vedotin (Adcetris)

- For the treatment of patients with classical HL after failure of autologous hematopoietic stem cell transplantation (auto-HSCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not auto-HSCT candidates
- For the treatment of patients with classical HL at high risk of relapse or progression as post-auto-HSCT consolidation
- For the treatment of patients with systemic anaplastic large cell lymphoma after failure of at least one prior multi-agent chemotherapy regimen

BISPECIFIC ANTIBODIES

Bispecific antibodies are engineered hybrid molecules with two unique binding domains, each of which recognizes a certain target unlike monoclonal antibodies that have two arms that both recognize the same target antigen.

Blinatumomab (Blinicyto)

- For the treatment of adults and children with relapsed or refractory B cell precursor ALL. The drug binds to CD3 on T cells and the CD19 antigen on tumor cells.



CELLULAR THERAPY

CAR T-CELL THERAPY

Adoptive cellular therapies include the chimeric antigen receptor (CAR) T-cell therapies. These directly provide engineered molecules called chimeric antigen receptors (CARs). T cells are removed from patients and genetically modified to produce CARs. The genetically engineered CAR T cells are grown in the laboratory until they number in the billions and are then infused back into the patient where they recognize and destroy cells with specific antigens on their surface that serve as the target.

Axicabtagene Ciloleucel (Yescarta)

- Axicabtagene ciloleucel is a CAR T-cell therapy directed to the CD19 antigen which is present on some lymphoma cells. It was approved by the FDA in October 2017 for the treatment of relapsed (returns after treatment) or refractory (does not respond to treatment) large B-cell lymphoma after two or more lines of systemic (throughout the body) therapy, including DLBCL, not otherwise specified;

primary mediastinal large B-cell lymphoma; high-grade B-cell lymphoma; and DLBCL arising from follicular lymphoma.

Tisagenlecleucel (Kymriah)

- The CAR T-cell therapy tisagenlecleucel is also directed against CD19. It was approved by the FDA in May 2018 for the treatment of relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including DLBCL, not otherwise specified; high grade B-cell lymphoma; and DLBCL arising from follicular lymphoma

CHECKPOINT INHIBITORS

Checkpoint inhibitors, such as nivolumab (Opdivo) and pembrolizumab (Keytruda), are a new class of drugs that have recently been introduced for lymphoma. "Checkpoints" are normally used by the immune system to determine whether or not to launch an immune response. Some cancers activate signaling via checkpoint proteins, such as CTLA-4 and PD-1/PD-L1, which are normally used to shut down immune responses against the body's own cells. By activating these checkpoints, cancers evade detection by the immune system as something that is bad for the body. Checkpoint inhibitors block this checkpoint activation (e.g., both nivolumab and pembrolizumab interfere with the PD-1/PD-L1 checkpoint), thereby restoring the immune system's ability to launch an attack against the cancer cells and rid them from the body. They are given intravenously. The most common side effects associated with checkpoint inhibitors include fatigue, upper respiratory tract infection, fever, diarrhea, and cough. Nivolumab and pembrolizumab have both been approved by the FDA for the treatment of relapsed or refractory classical Hodgkin lymphoma (HL).

Nivolumab (Opdivo)

- For the treatment of patients with classical HL that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and post-transplantation brentuximab vedotin (Adcetris)

Pembrolizumab (Keytruda)

- For the treatment of patients with refractory classical HL or who have relapsed after three or more prior lines of therapy.

CYTOKINES

Cytokine drugs, such as interferon alfa-2b (Intron A) and denileukin diftitox (Ontak), are synthetic versions of naturally occurring cytokines (proteins used by immune system cells to communicate with each other). They are not commonly used today for the treatment of lymphoma. Cytokine drugs boost the body's immune response to lymphoma cells. They may be given subcutaneously or intravenously. Common side effects of cytokines include flu-like symptoms, low white cell counts, rashes, and thinning hair.

Denileukin Diftitox (Ontak)

- For the treatment of patients with persistent or recurrent cutaneous T-cell lymphoma whose malignant cells express the CD25 component of the IL-2 receptor

IMMUNOMODULATORY DRUGS

Immunomodulatory drugs (IMiDs), such as lenalidomide (Revlimid), have many ways of working against tumor cells. They cause tumor cells to die, help keep tumors from getting nutrients from the blood and tumor microenvironment, and stimulate the immune system. This drug is given orally, in capsule form. The most common side effects of lenalidomide are low blood cell counts, fatigue, diarrhea, nausea, cough, fever, rash, shortness of breath, itching, constipation, and swelling, with a small increase in the risk of blood clots.

Lenalidomide (Revlimid)

- Treatment of patients with mantle cell lymphoma (MCL) whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib (Velcade). In combination with rituximab for relapsed or refractory follicular and marginal zone lymphoma.

Interferon Alfa-2b (Intron A)

- For the initial treatment of clinically aggressive follicular NHL in conjunction with anthracycline-containing combination chemotherapy in patients 18 years of age or older. This drug is rarely used anymore.

MONOCLONAL ANTIBODIES

Many of the immunotherapies used to treat lymphoma are monoclonal antibodies. An antibody is a protein that binds to a single type of molecule, such as another protein. Each type of antibody therefore has a unique target. Lymphoma cells have proteins on their surfaces called CD (cluster of differentiation) proteins; examples include CD20 and CD52. Many of the antibodies used to treat lymphoma were designed to recognize and bind to these CD proteins. When they do, they either destroy the cell directly or recruit the individual's own immune system to destroy lymphoma cells. Examples of FDA-approved antibodies used to treat lymphoma include rituximab (Rituxan), obinutuzumab (Gazyva), and ofatumumab (Arzerra). All monoclonal antibodies are given either intravenously or subcutaneously. Common side effects of monoclonal antibodies include allergic reactions, fever, chills, weakness, headache, nausea/vomiting, diarrhea, low blood pressure, chest tightness, and rashes.

Rituximab (Rituxan)

For the treatment of patients with:

- Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell non-Hodgkin Lymphoma (NHL) as a single agent
- Previously untreated follicular, CD20-positive, B-cell NHL in combination with firstline (initial) chemotherapy and, in patients achieving a complete or partial response to rituximab in combination with chemotherapy, as single-agent maintenance therapy
- Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after firstline CVP (cyclophosphamide, vincristine, prednisone) chemotherapy
- Previously untreated diffuse large B-cell, CD20-positive NHL in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or other anthracycline-based chemotherapy regimen

- In combination with fludarabine (Fludara) and cyclophosphamide (FC), for the treatment of patients with previously untreated and previously treated CD20-positive chronic lymphocytic leukemia (CLL)

Rituximab and Hyaluronidase Human (Rituxan Hycela)

A subcutaneous form of rituximab was approved by the FDA in 2017 for use in patients with previously untreated DLBCL, and those with previously untreated and relapsed or refractory follicular lymphoma or CLL. Before patients can receive rituximab and hyaluronidase human (Rituxan Hycela), they must first have at least one full dose of IV rituximab. Dosing of subcutaneous rituximab varies depending on the type of lymphoma being treated.

Obinutuzumab (Gazyva)

- In combination with chlorambucil (Leukeran) for the treatment of patients with previously untreated CLL
- In combination with bendamustine (Treanda) followed by obinutuzumab monotherapy for the treatment of patients with follicular lymphoma (FL) who relapsed after, or are refractory to, a rituximab (Rituxan)-containing regimen
- In combination with chemotherapy followed by obinutuzumab monotherapy in patients achieving at least a partial remission, for the treatment of adult patients with previously untreated stage II bulky, III or IV follicular lymphoma

Ofatumumab (Arzerra)

- In combination with chlorambucil, for the treatment of previously untreated patients with CLL for whom fludarabine (Fludara)-based therapy is considered inappropriate
- In combination with fludarabine and cyclophosphamide for the treatment of patients with relapsed CLL
- For extended treatment of patients who are in complete or partial response after at least two lines of therapy for recurrent or progressive CLL
- For the treatment of patients with CLL refractory to fludarabine and alemtuzumab (Campath)

Polatuzumab Vedotin-Piiq (Polivy)

In combination with bendamustine and rituximab for the treatment of patients with diffuse large B-cell lymphoma who have failed at least two prior regimens.

Radioimmunotherapy

Radioimmunotherapy (RIT) consists of a monoclonal antibody attached to a source of radiation. RIT acts as a "guided missile" to destroy lymphoma cells by attaching to a specific molecule on the surface of the lymphoma cell, such as CD20, and delivering small doses of radioactivity, which is intended to kill the cell. The only FDA-approved RIT for lymphoma is ibritumomab tiuxetan (Zevalin). RIT is given intravenously. Side effects of RIT include fever/chills, pneumonia, lung inflammation, arrhythmias, and low blood counts.

Ibritumomab Tiuxetan (Zevalin)

- For the treatment of relapsed or refractory, low-grade or follicular B-cell NHL
- For the treatment of previously untreated follicular NHL in patients who achieve a partial or complete response to first line chemotherapy

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IMMUNOTHERAPIES UNDER INVESTIGATION FOR LYMPHOMA

Several other classes of immunotherapies are currently in clinical trials:

- Antibodies that target CD19 include MEDI551 and MOR00208 (Tafasitamab)
- Antibodies that target CD74 include milatuzumab
- Antibodies that target CD79 include polatuzumab vedotin
- Antibodies that target CD137 include urelumab
- Antibodies that target CCR4 include mogamulizumab
- Antibodies that target OX40 include MEDI6469
- Antibodies that target CD47
- Checkpoint inhibitors include atezolizumab (Tecentriq) and CA-170
- JCAR017 that targets AntiCD19 CAR T Cells
- AntiCD22 CAR T cells
- AntiCD20 CAR T cells
- AntiCD30 CAR T cells

VACCINES

Cancer vaccines that stimulate the immune system to fight lymphoma cells are also being evaluated in clinical trials, including:

- CDX-301
- Imprime PGG



QUESTIONS TO ASK YOUR DOCTOR

- What is the goal of my immunotherapy treatment?
- What are the risks, possible side effects, and benefits of the immunotherapy I will receive?
- What symptoms should I expect? Which of these should prompt me to seek medical attention?
- What side effects should I expect? Which of these should prompt me to seek medical attention?

- What should I do to take care of myself before and during treatment?
- How long will each treatment session last?
- How long will the entire treatment process last?
- What are the chances that the treatment will be successful?
- How will the treatment affect my normal activities (eg, work, school, childcare, driving, sexual activity, exercise)?
- Will I be able to work during treatment?
- How often will I need a checkup?
- How much will the treatment cost? Will my insurance cover it?
- Will a particular immunotherapy impact potential future treatment decision?

Clinical Trials Information Service

Clinical trials are crucial in identifying effective drugs and determining optimal doses for patients with lymphoma. Patients interested in participating in a clinical trial should view the Understanding Clinical Trials fact sheet on LRF's website at www.lymphoma.org, talk to their physician, or contact the LRF Helpline for an individualized clinical trial search by calling 800-500-9976 or emailing helpline@lymphoma.org

Education Resources

- In-Person Education Programs
- Focus on Lymphoma Mobile App
- Patient Publications
- Podcasts
- Webinars
- YouTube Videos

Support Services

- Financial Assistance Program
- LRF Helpline
- Lymphoma Support Network
- Stories of Hope

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